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Resistant pneumococcal infections

Stephanie J. Schrag,
Bernard Beall and
Scott Dowell



World Health Organization

Resistant pneumococcal infections: the burden of disease and challenges in monitoring and controlling antimicrobial resistance

Stephanie J. Schrag, Bernard Beall and Scott Dowell

*Respiratory Diseases Branch
Centers for Disease Control and Prevention
Atlanta, GA, United States of America*



World Health Organization

A BACKGROUND DOCUMENT FOR
THE WHO GLOBAL STRATEGY
FOR CONTAINMENT OF
ANTIMICROBIAL
RESISTANCE

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Executive Summary

Acute respiratory infections (ARI) are a leading cause of childhood mortality, causing 25–33% of all deaths in children in developing countries. Bacterial ARI are associated with higher case-fatality ratios than infections caused by viruses. *Streptococcus pneumoniae* is the most common cause of bacterial ARI, and pneumococcal resistance is the principal cause for concern regarding treatment failures for ARI and meningitis. Therefore, this review focuses on pneumococcal resistance.

ARI are often treated empirically with antibiotics. Drug-resistance trends are not well documented in most developing countries due to limited laboratory capacity. It is clear, however, that the prevalence of strains resistant to penicillin-related compounds and to co-trimoxazole is increasing. The clinical impact of pneumococcal resistance varies with the site of infection and is better documented for meningitis and otitis media than for pneumonia.

The ecological niche of *S. pneumoniae* is the human nasopharynx, where it can be carried asymptomatically and transmitted from person to person. Children carry *S. pneumoniae* more commonly than adults. In contrast to a majority of other pathogens where drug resistance is a problem, the evolution of drug resistance within a patient during the course of antibiotic therapy is not common in *S. pneumoniae*. This is because resistance conferred by single-point mutations alone is rare in pneumococcal clinical isolates. Transformation (the uptake of free DNA from the environment) and conjugative transposons (the transfer of segments of genomic DNA during bacterial fusion) are the two primary genetic mechanisms conferring pneumococcal resistance.

Epidemiological studies have demonstrated that recent antibiotic use is strongly associated with carriage of resistant pneumococci both at the community and individual levels. Among individuals who develop invasive pneumococcal disease, recent antibiotic use is also associated with an increased risk of infection with a resistant strain. The biological mechanisms behind the association between recent

antibiotic use and carriage of resistant strains are not completely understood and require further research.

A key factor influencing the emergence and spread of resistant pneumococci is unnecessary antibiotic use for viral respiratory illnesses in humans. This is due to misdiagnosis of conditions because both viral and bacterial agents can cause symptoms of ARI, as well as physician and patient pressures to prescribe antibiotics. However, while antibiotic overuse is a problem in some developing settings, in others, poor access to adequate health care is still a primary problem and children requiring antibiotic therapy do not receive it.

Pneumococcal resistance can also be inadvertently driven by the use of drugs for unrelated conditions. This may pose a particularly serious problem as mass antibiotic prophylaxis campaigns to eliminate trachoma are introduced in a number of African countries.

To date, the pneumococcal polysaccharide vaccine is the principal established intervention to protect against pneumococcal disease. Because this vaccine only protects against bacteraemic pneumococcal pneumonia, is not indicated for children under 2 years of age, and has no impact on pneumococcal carriage, it is not an effective intervention against ARI or the spread of drug resistance in most developing countries.

A pneumococcal conjugate vaccine has now been approved for routine infant use in the United States. This vaccine has been shown to be highly effective at preventing pneumococcal pneumonia and meningitis in young children and infants. Moreover, the vaccine has some efficacy at protecting against otitis media, and also protects against carriage of vaccine-included pneumococcal serotypes. Because of its unique features, this vaccine holds great potential as an “anti-resistance vaccine” which simultaneously reduces the burden of invasive disease and the prevalence of resistant strains. Prophylactic use of xylitol, a sugar which inhibits pneumococcal growth, may also represent a feasible intervention against non-invasive disease and resistance in developing countries.

Top 5 research recommendations

1. Develop rapid, inexpensive methods for detecting resistance (*Section C*)
2. Assess the impact of antibiotic control programmes on pneumococcal resistance (*Section D*)
3. Assess the disease burden due to pneumococcal resistance to help evaluate the feasibility of expensive but effective interventions (*Sections A, E*)
4. Study the impact of mass azithromycin prophylaxis against trachoma on pneumococcal resistance (*Section D*)
5. Document the impact of the conjugate pneumococcal vaccines on the burden of disease due to resistant pneumococci (*Section E*)

A. Disease incidence and trends

1. Populations at risk

Streptococcus pneumoniae infections are a leading cause of illness in young children, the elderly and persons with debilitating medical conditions. Infections caused by *S. pneumoniae*, or “pneumococci”, can range from severe invasive disease such as pneumonia, meningitis and bacteraemia, to otitis media. In developing countries, *S. pneumoniae* and *Haemophilus influenzae* are the leading bacterial causes of acute respiratory infections (ARI) in children. *S. pneumoniae* can be isolated from approximately 30% of ARI patients where an etiology is identified and is associated with significantly higher case-fatality ratios than viral causes of ARI (1, 2). Globally, *S. pneumoniae* is associated with an estimated 1 million deaths each year in children less than 5 years of age (3).

Studies in developing countries have identified malnutrition and exposure to cigarette or cooking fire smoke as risk factors for pneumococcal infection (4). HIV infection is also associated with an increased risk of severe pneumococcal illness in both children (5) and adults (6). Additionally, a high incidence of pneumococcal disease has been associated with crowding in adult communities, such as South African mining communities (7). In some studies males have had higher rates of disease than females (8). In children, breast-feeding has been found to be protective (4). Rates of invasive pneumococcal disease in the United States are higher in blacks and Native Americans than in whites, and higher in males than in females (9, 10, 11).

2. Geographical distribution

(See Tables 1 and 2 for a summary)

Africa

Detailed data exist for the Gambia. The incidence of pneumococcal disease in the Western part of the Gambia is 82-224/100 000 child years for children under 3 years, 2 to 8 times higher than that reported for Finland, Israel or the United States (12). In the Gambia, pneumococcus was the causative agent in 69% of all childhood pneumonia cases

where a bacterial pathogen was identified (8); pneumococcus was also associated with approximately 50% of cases of pyogenic meningitis (12). Pneumonia is the most common clinical presentation; 95% of cases of pneumococcal disease present as pneumonia or meningitis.

Asia

Limited data are available on rates of carriage and disease in Asia. The vast majority of data is not population-based, and focuses on invasive isolates. Estimates of disease incidence cannot be obtained directly from such data.

Australia/New Zealand

Rates of pneumococcal carriage and invasive disease are particularly high in Pacific Islanders and aboriginal populations in Australia and New Zealand (13, 14, 15). The rate of pneumococcal meningitis in infants in Auckland, New Zealand is 32/100 000 (16).

Industrialized countries (detailed data exist for France, Israel, Scandinavia, the United States)

Otitis media and bacteraemia without focus are the most common presentations. In the United States, where active surveillance data are available from selected states, infection due to *S. pneumoniae* is estimated to result in 3000 cases of meningitis, 50 000 cases of bacteraemia, 125 000 cases of hospitalized pneumonia and 7 million cases of otitis media (17). Rates of pneumococcal meningitis in infants have been measured by population-based surveillance in a number of countries: Finland: 6.8/100 000 (18); USA: 15.7/100 000 in infants <1 month and 6.6/100 000 in children 1–23 months (19); Israel: 16.7/100 000 (20). Rates of pneumococcal disease are significantly higher in infants native of Alaska than in other racial groups in the United States; the rate of pneumococcal meningitis in this population is approximately 138/100 000.

TABLE 1. THE INCIDENCE OF PNEUMOCOCCAL MENINGITIS IN INFANTS IN SELECTED COUNTRIES

Country	Incidence per 100 000 population*	Reference
Finland	7	(18)
Israel	17	(20)
United States of America	16: <1 month 7: 1–23 months	(19)
Santiago, Chile	27	(21)
Auckland, New Zealand	32	(16)
Central Australia: Aboriginal population	101 **	(101)
Alaskan Natives	138	(9)
The Gambia	148	(8)
Niamey, Niger	150	(24)

* In children <1 year of age unless otherwise stated.

** Incidence in children <5 years of age.

Latin America

A study of invasive pneumococcal disease in infants in Chile found that disease incidence in infancy was 60.2 per 100 000 (21). The rate of pneumococcal meningitis in infants in Santiago, Chile is approximately 26.7/100 000 (21). A Pan American Health Organization study of invasive pneumococcal infection in children in six Latin American countries estimated that pneumonia represented 50% of disease (22).

3. Adequacy and quality of data documenting disease

Population-based surveillance founded on laboratory-confirmed invasive disease is the best method for accurately estimating rates of pneumococcal disease. This requires census data for the population under surveillance as well as laboratory isolation of *S. pneumoniae* from a normally sterile site from patients with suspected pneumococcal disease. Some industrialized countries, such as the United States, have the resources to conduct active, population-based surveillance for invasive pneumococcal disease. In contrast, data from developing countries come primarily from hospital studies or surveillance for clinical syndromes compatible with pneumococcal infections such as pneumonia or ARI. Consequently, estimates of disease rates in developing and developed countries should be compared with caution. The most straightforward rates to compare are those for pneumococcal meningi-

tis, which is likely to result in hospitalization in most countries (21) (Table 1).

Developing countries can rarely conduct population-based surveillance for pneumococcal disease, in part because adequate demographic data are not always available. The primary difficulty in conducting surveillance in developing countries, however, is establishing the etiology of outpatient respiratory infections. This requires laboratory culture of pneumococcus, which can be a challenge in a developing country setting (23). Moreover, the sensitivity of blood culture for identifying pneumococcal pneumonia is typically low (10–30%), and lung puncture is more invasive. In addition, it can be hard for laboratories with few facilities to rule out viral infections because laboratory culture is difficult, antigen detection tests are not widely available, and serology in children may be insensitive. Finally, while blood cultures are commonly collected from febrile infants in industrialized countries they often are not collected from children in developing countries.

In light of these difficulties, developing countries may elect to follow one of the following alternatives to active, population-based surveillance for invasive pneumococcal disease. Choice among the alternatives may be guided by resources available and goals of surveillance. (1) Point-prevalence nasopharyngeal carriage survey of selected populations (e.g. outpatients at a local clinic or children in a particular city or village). This is a low-cost method that sheds light on the prevalence of resistant strains in the community; because most carried strains do not result in invasive disease, this method may overestimate the burden of resistance and does not provide information on the burden of invasive disease. (2) Hospital-based surveillance of invasive isolates. This method has been widely used by the Pan American Health Organization in Latin America. It is useful for identifying the serotypes and resistance profiles of strains associated with invasive disease. Because it is not population-based it does not help estimate the burden of invasive disease; moreover, because it focuses on isolates obtained from hospitalized patients, information on invasive outpatient cases is lost. (3) Population-based surveillance for bacterial meningitis. This method, which has been used successfully in developing country settings (24) allows direct estimation of the rate of pneumococcal and other forms of bacterial meningitis. It is labour-intensive because it involves culturing all CSF specimens, and obtaining results from all hospitals within an area, but more feasible

than surveillance for all invasive disease because meningitis patients are almost always hospitalized.

4. Diagnosis: methods, feasibility, accuracy, overlapping clinical syndromes

Clinical diagnosis

In developing countries, WHO developed an algorithm for diagnosing ARI as part of the Integrated Management of Childhood Illness initiative (IMCI) (25). The diagnostic criteria are broad and are aimed to capture all cases of illness requiring urgent treatment. For the case of children presenting with fever, any general danger sign and/or stiff neck, very severe febrile disease such as malaria or meningitis is considered the diagnosis. For the case of children presenting with cough or difficult breathing, the following diagnoses are recommended. A child with documented tachypnea is considered to have severe pneumonia if any general danger signs, chest indrawing, or stridor are present. A child presenting with tachypnea but no danger signs is considered to have pneumonia; if the only symptoms present are cough or difficult breathing, the child is considered to have a cough or cold. For children with symptoms related to the ear, tender swelling behind the pinna is classified

as mastoiditis; visible pus discharge from the ear canal for less than 14 days is classified as an acute ear infection; similar symptoms for more than 14 days are classified as a chronic ear infection.

Laboratory diagnosis

Laboratory diagnosis of pneumococcal infections can be difficult, and the vast majority of pneumonia, meningitis and otitis media cases in developing countries are treated empirically without identifying the etiological agent. For the case of pneumonia, blood culture is the gold standard method of identification. Blood culture is also recognized as overly restrictive because it may exclude as many as 75% of pneumococcal pneumonia cases. Sputum Gram's stain and culture are also good methods when adequate specimens are obtained, which is rare for children. For the case of meningitis, there are no clinical features of pneumococcal meningitis that distinguish it reliably from other forms of meningitis. Gram's stain of CSF specimens and culture is highly accurate if a patient has not received prior antimicrobial therapy. The causative agent of otitis media can be identified by tympanocentesis, but this procedure is rarely performed even in industrialized countries unless a child fails to respond to antimicrobial therapy.

TABLE 2. AGE-SPECIFIC PREVALENCE OF PNEUMOCOCCAL CARRIAGE IN DIFFERENT GEOGRAPHICAL REGIONS

Country	Population sampled	Study design	Age	Prevalence of nasopharyngeal carriage	N	Reference
Zambia	Children attending a paediatric outpatient clinic, Lusaka	Cross-sectional	3 months 12 months 24 months 3–6 years	80% 73% 75% 50%	260	(102)
Israel	Healthy children	Longitudinal	2 months 12 months 24 months	26% 39% 62%	514	(63)
Costa Rica	Healthy children in a rural, concentrated population	Longitudinal	1 month 12 months	3.3% 20%	339	(29)
USA	Healthy infants, Birmingham, AL	Longitudinal		Mean age of first acquisition: 6 months	82	(27)
	Children residing in Shelby County, TN	Cross-sectional	< 6 years (median=22 months)	47%	216	(66)
Australia	Infants in a remote aboriginal community	Longitudinal		Mean age of first carriage: 163 days (range: 20–399 days)		(15)
Papua New Guinea	Neonates from urban and periurban villages	Longitudinal		100% of infants had been colonized by 80 days of age	25	(13)
Iceland	Children in 5 geographical areas	Cross-sectional	< 2 years 2–6 years	47.9% 54.3%	919	(57)

5. Organisms causing the disease

Both viral agents (e.g. respiratory syncytial virus and parainfluenza virus), and bacterial agents (primarily *S. pneumoniae*, *H. influenzae*), can cause pneumonia, meningitis and otitis media. This review focuses primarily on *Streptococcus pneumoniae*, a Gram-positive bacterium. Over 90 known serotypes have been identified based on antigenic differences in the capsular polysaccharide.

6. Ecological niche of the organisms

The human nasopharynx is the primary reservoir for *S. pneumoniae*, and is the main source of person-to-person transmission. Pneumococcal infections are preceded by bacterial colonization of the nasopharyngeal mucosa (26, 27) where the bacteria can persist as part of the extracellular flora without causing disease. The nasopharyngeal flora is complex, consisting of normally non-pathogenic bacteria such as aerobic α -haemolytic streptococci, anaerobic streptococci and *Prevotella melaninogenica*, in addition to potential respiratory pathogens such as *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (28).

Nasopharyngeal carriage of *S. pneumoniae* is more common in young children than adults, and varies by geographical region (Table 2). In a study of 25 neonates in urban and periurban villages in Papua New Guinea, the mean age of acquisition of pneumococcal carriage was 17 days, with the earliest colonization event occurring on day 1 post birth (13). In contrast, a longitudinal study of the acquisition and carriage of *S. pneumoniae* in 82 children followed from birth in Birmingham, Alabama, United States (27) found that the mean age of first carriage was 6 months. Variation in the prevalence of nasopharyngeal carriage may be due to genetic differences affecting the likelihood of nasopharyngeal colonization and also to socioeconomic conditions such as crowding, sanitation, family size, day-care contact, and access to health care (29). Carriage of multiple serotypes or strains within a serotype has been documented, particularly in regions where the prevalence of nasopharyngeal carriage is high. In a study of 175 healthy children from different regions of Papua New Guinea, 46 of 156 children positive for *S. pneumoniae* (29.5%) were found to carry multiple serotypes, including three children carrying triple populations (14). One additional child carried two strains of the same serotype that had significantly different MICs for penicillin. Other studies have documented carriage

of multiple serotypes in Australian aboriginal children (15, 30) and in male military personnel (31). Because the methods for screening for multiple serotypes are labour-intensive, the prevalence of carriage of multiple pneumococcal strains and serotypes is not well characterized in a majority of populations.

The duration of carriage varies widely, depending in part on the host's age and on the serotype of the colonizing strain. The duration of the first carriage event experienced by a group of infants born in Papua New Guinea (13) ranged from 5 to 290 days. Similarly, in a longitudinal study of Alabama infants, carriage duration ranged from 1 to 17 months, with longer durations associated with the first colonization event (27). Colonization during the first two years of life is predominantly associated with serogroups 6, 14, 19 and 23 (32). These serogroups, sometimes referred to as "childhood" or "paediatric" strains, are also associated with longer durations of carriage, and rapid reacquisition in young children.

Smith et al. (33) estimated the acquisition and elimination rates of individual serotypes, based on data from a longitudinal carriage study of children in Papua New Guinea. Using a catalytic modelling approach, they found that pneumococcal serotypes varied widely in acquisition and loss rates, and therefore, in the mean duration of carriage. In Papua New Guinea children, serotype 6 was the most frequently acquired and the most persistent strain. This study also found that serotypes with higher acquisition rates and longer durations of carriage had a stronger association with invasive disease.

Factors responsible for the transition from carriage to disease remain poorly understood. In the longitudinal study of Alabama infants, 15% of colonization events resulted in infection (27). Disruption of natural barriers, for example due to damaged bronchial epithelium following influenza infection, can lead to invasive pneumococcal infections (3). Some viruses and cytokines also enhance bacterial adherence *in vitro* and may have a similar effect *in vivo* (3). Additionally, some strains of *S. pneumoniae* have virulence determinants, for example alterations to the capsular polysaccharide, that enhance their likelihood of causing disease by preventing phagocytosis. Improving the understanding of why some children remain asymptomatic carriers but others develop severe invasive disease may help in evaluating the effects of xylitol, vaccines and other approaches to prevention (see Section E).

7. Data on current drug-resistance trends and problems

Drug-resistance trends

Because methods of conducting surveillance for pneumococcal resistance have not been standardized, comparisons using studies from different countries are difficult. In particular, surveillance data typically are based on sterile site isolates from hospitalized individuals or non-sterile site isolates from randomly selected children and adults in the community. Although sterile site isolates shed light on the strains directly associated with invasive disease, culture methods are more complicated and typically result in a lower yield, particularly in developing countries. Moreover, screening based on sterile-site isolates is biased towards individuals attending tertiary care facilities. For example, the percentage of penicillin-resistant invasive isolates from single hospitals within a state in the United States did not reflect the mean prevalence of penicillin resistance for the state as a whole, as estimated by population-based surveillance (34).

In contrast, nasopharyngeal isolates have a higher yield and are collected directly from the site associated with person-to-person transmission. However, not all pneumococcal strains isolated from the nasopharynx are associated with invasive disease. A number of studies in developing countries comparing pneumococcal resistance in isolates obtained from blood and from nasopharyngeal swabs have found that nasopharyngeal carriage isolates approximate the antibiotic-resistance rates found in invasive isolates (35, 36, 37, 38). Oropharyngeal cultures, however, have a much lower yield than nasopharyngeal isolates and should not be used.

Despite limitations in the available surveillance data, some robust trends are evident. One of the most striking is geographical variation in the prevalence of antimicrobial-resistant pneumococci. In the 1970s penicillin-resistant pneumococci were most common in Israel, Papua New Guinea, Poland, South Africa and Spain as well as some states in the United States (39). Now resistant pneumococci have a worldwide distribution, although only limited surveillance data from a majority of African, Asian and South American countries are available. A recent survey of clinical specimens from 11 Asian countries from 1996 to 1997 found that penicillin non-susceptibility ranged from 80% of isolates in the Republic of Korea to 4% of isolates in India (40). A detailed study of invasive isolates from six hospitals in India found penicillin non-suscepti-

bility in 1.3% of isolates; resistance to trimethoprim/sulfamethoxazole was present in 56% of isolates, and to chloramphenicol in 17% of isolates (41). In Europe, Spain is a focus of penicillin-non-susceptible pneumococcal strains, with a prevalence of non-susceptibility of over 45% of pneumococcal isolates (39). A high incidence of resistance has similarly been reported for Eastern European countries.

A smaller but growing number of isolates are also resistant to multiple antibiotics and some are susceptible only to parenteral agents (17), posing a threat to the effective treatment of pneumococcal disease.

Clinical impact of resistance

It is difficult to measure the impact of infection with a resistant strain on increased morbidity and mortality for a number of reasons. First, it is often not possible to control for risk factors such as underlying disease that confound the association with mortality. Second, resistant pneumococci can vary greatly in their degree of resistance to a particular drug. Resistance is typically measured as MIC, the minimal concentration of antibiotic required to inhibit bacterial growth. The clinical impact of strains with an intermediate MIC may be much less than that of a highly-resistant strain. Third, the clinical impact of antibiotic resistance varies with the site of infection, the ability of antibiotics to penetrate to that site, and the ability of the immune response to clear the infection. Consequently, we consider the major clinical syndromes caused by *S. pneumoniae* individually.

Meningitis. Antibiotic resistance poses a particular problem for the case of meningitis because most antibiotics do not penetrate effectively into the cerebrospinal fluid (CSF). Because penicillin-resistant pneumococcal meningitis has become common (32), the extended-spectrum cephalosporins are widely used for treatment of meningitis. Treatment failures due to infection with cephalosporin-resistant pneumococcus, however, have now been reported in both children (42, 43) and adults (44, 45). In a rabbit meningitis model, penicillin-resistant pneumococci were eradicated from the site of infection only if the antibiotic concentration in CSF exceeded the lowest concentration of drug required to kill pneumococci by 8- to 10-fold (46). Such levels are difficult to achieve, particularly as MICs increase. Similarly, an *in vitro* study (47) of the efficacy of high-dose cefotaxime against interme-

diate and high-level cephalosporin-resistant pneumococci found that only 44% (8/18) of CSF samples obtained from meningitis patients exposed to a high dose of cefotaxime achieved 99.9% killing of pneumococci with high-level resistance. This study demonstrated wide variation among patients in antibiotic pharmacokinetics in the CSF. In response to growing numbers of treatment failures, the American Academy of Pediatrics recommends that children with possible pneumococcal meningitis be treated with a combination of vancomycin plus cefotaxime or ceftriaxone (48). Animal models have shown that this combination therapy produces a synergistic effect (49).

Otitis media. There is now clear evidence that acute otitis media treatment failures have been directly attributable to resistant pneumococci. For example, in a study of 78 children under 3 years of age with acute otitis media caused by *S. pneumoniae*, only 6% of children infected with a cephalosporin-susceptible strain had bacteriological treatment failures following cephalosporin treatment while 35% infected with a strain of intermediate resistance had bacteriological failures (50). Drugs with a lower activity against pneumococci, such as cefaclor and cefixime, are affected more by increasing MICs than drugs such as amoxicillin (50). In response to the rapid dissemination of drug-resistant *S. pneumoniae*, the Drug Resistant *S. pneumoniae* Therapeutic Working Group (Appendix) recently recommended that amoxicillin remain the first-line antibiotic for acute otitis media, but that the dosage should be routinely doubled, and that clinical failures after 3 days of therapy require an alternative agent effective against resistant *S. pneumoniae* and β -lactamase producing pathogens (51). Antibiotic therapy is recommended for acute otitis media primarily to protect against rare but severe sequelae of such infections. Up to 80% of cases of otitis media from all causes resolve without treatment (52).

Pneumonia. Evidence for treatment failures due to antibiotic-resistant pneumococcal pneumonia has been more difficult to document. A number of studies in adults and in children have found that pneumococcal resistance did not influence the outcome of pneumonia treatment (45). These studies, however, included patients with low levels of β -lactam resistance (MIC <1 μ g/ml). Standard treatment for pneumococcal pneumonia has been shown to be effective against both susceptible strains and strains of intermediate resistance. For strains with high-level resistance to penicillin (MICs >4 μ g/ml)

clinical and pharmacodynamic data suggest that increased mortality or complications are likely. An analysis of population-based active surveillance for pneumococcal pneumonia from nine areas in North America found that mortality was associated with penicillin MICs ≥ 4 and cefotaxime MICs ≥ 2 , only after the first four days of hospitalization were excluded (53). Mortality in the first four days of illness, which occurred for almost half of pneumococcal pneumonia-associated deaths, is influenced by the severity of presenting illness rather than any particular therapeutic intervention. Because resistant strains do not typically alter illness presentation (52) increasing levels of resistance may not affect mortality rates in the early stages of illness. Pharmacokinetic/pharmacodynamic evidence suggests that β -lactams might not be effective at treating pneumococcal strains with penicillin MICs >8 and cefuroxime MICs >4.

8. Summary: Disease incidence and trends

- There is a need for better data on the global burden of pneumococcal disease. Such information can be obtained by surveillance for nasopharyngeal carriage in children, or by focusing on clinical isolates. These data are difficult to obtain for a number of reasons: surveillance systems for invasive disease are not in place in many developing countries; the etiological agents causing pneumonia, meningitis and otitis media are rarely identified; the clinical syndromes associated with pneumococcal disease overlap with those caused by a wide range of other pathogens. Moreover, comparisons across countries are difficult because the threshold for seeking health care and for performing diagnostic procedures varies greatly.
- Efforts to assess the pneumococcal disease burden are also important to help evaluate effective but costly interventions such as conjugate vaccines, antibiotic use control programmes, and others (discussed in section E). Because antimicrobial resistance concerns overlap with intervention concerns, efforts to characterize disease burden should be coordinated.
- There is a need for better data on drug resistance in developing countries. Surveillance for drug resistance not only better characterizes the magnitude of the problem but often also leads to increased awareness of the issue and develops important local laboratory capacity. Surveillance

for nasopharyngeal carriage rather than focusing strictly on clinical isolates has been recommended recently by WHO. However, these methods have still not been field-tested, and whether population-based surveillance is worth the added expense depends on the burden of resistant disease and impact relative to other priorities.

- Treatment failures due to pneumococcal resistance have been documented for meningitis and otitis media. The clinical impact of resistance in the treatment of pneumonia has been more difficult to establish. Because pneumonia causes a much more significant burden of disease than otitis media in many developing countries, understanding how antibiotic resistance affects pneumococcal pneumonia management should remain a priority.

9. Research needs: Disease incidence and trends

1. Develop generic protocols for assessing the burden of pneumococcal disease in developing countries.
2. Assess the disease burden due to pneumococcal resistance to prioritize possibly expensive but effective interventions such as conjugate vaccines, antibiotic use control programmes and others (discussed in section E).
3. Compare surveillance for resistant nasopharyngeal carriage to surveillance for resistant clinical isolates. Studies should focus on identifying conditions when population-based surveillance is required, and when point-prevalence clinic-based surveys will suffice.
4. Monitor trends in resistance to new or important antibiotic agents besides penicillin. These include: macrolides, co-trimoxazole and quinolones.

B. Causes of resistance

1. Mechanisms of resistance

The genetic basis of resistance plays a key role in determining how resistance develops and spreads within communities. A number of biological features distinguish pneumococci from other pathogens with acquired drug resistance, such as *Mycobacteria*, and *Escherichia coli*. First, resistance in clinical pneumococcal isolates is rarely due to single-point mutations alone or to plasmid carriage. Second, transformation (the uptake and chromosomal exchange of free DNA from closely related strains or species), and conjugative transposons (transfer and genetic incorporation of small segments of DNA during bacterial fusion events) are the most common mode for pneumococci to acquire resistance genes. Third, pneumococci are commonly carried asymptomatically in the nasopharynx, which is also the source of person-to-person transmission. Fourth, resistant strains can differ in their degree of resistance to a particular drug, measured as the MIC (minimum inhibitory concentration of a particular antibiotic).

These biological characteristics directly influence the population dynamics of pneumococcal resistance. Because resistance seldom results from single-point mutations alone (single DNA base changes that occur due to errors during bacterial replication), evolution of resistant pneumococci within a patient during the course of antibiotic treatment rarely occurs. Instead, resistant pneumococcal infections result primarily from the acquisition of resistant strains from the community. Moreover, because the preconditions for acquiring resistance by transformation and conjugative transposons are more stringent than those for point mutation, resistant pneumococci spread primarily by clonal amplification rather than repeated *de novo* generation. Finally, both infected individuals and asymptomatic carriers can transmit pneumococci. Thus, reducing the number of infected individuals in a population does not necessarily reduce the potential for transmission of resistant strains within the community.

The genetic mechanisms associated with different clinically-relevant antibiotic resistance phenotypes are summarized in Table 3.

Association between resistance and serotype

Currently, the vast majority of clinical isolates from the United States with high-level resistance to β -lactam antibiotics belong to serogroups 6, 9, 14, 19, and 23. These same serogroups are also often associated with β -lactam resistance in other countries. While the genetic diversity within each of these serotypes is striking, resistant isolates within each serotype typically belong to prevalent, well-documented clonal groups. A majority of these clonal groups have also acquired numerous other drug resistances, including resistance to erythromycin, chloramphenicol, trimethoprim/sulfamethoxazole, and tetracycline.

It is not yet clear why these particular serogroups have a higher probability of containing resistance genes. It is possible that transformation barriers play a role in preventing some serotypes from acquiring β -lactam resistance and other horizontally-spread resistance determinants. The proportion of clinical isolates that are transformable in the laboratory has not been determined. Optimal competence conditions differ between strains, and the capsule itself reduces or totally inhibits transformation. Cell wall barriers imposed by different capsular types, incompatible competence factors between donor and recipient strains, and host endonuclease restriction of incoming DNA might all limit the spread of resistance via transformation among specific serotypes.

Despite evidence of a strong association between resistance patterns and serotype, the gene-encoding capsular serotype can also be exchanged between strains by transformation (54). Thus, it is possible that highly resistant clones may become members of highly invasive serotypes that are currently not associated with multidrug resistance.

TABLE 3. GENETIC MECHANISMS OF PNEUMOCOCCAL ANTIBIOTIC RESISTANCE*

Phenotype	Genetic basis of resistance	Origin	Frequency among isolates resistant to that drug class	References
Intermediate β -lactam resistance	Penicillin-binding protein (PBP) gene alterations	Transformation with PBP genes from resistant, closely related species.	All known penicillin-resistant clinical isolates	(103, 104)
High-level penicillin resistance	PBP gene alterations	Sequential transformation events, which can also be followed by spontaneous mutation events conferring incremental resistance.	All known clinical isolates have mosaic structures for these 3 genes. Note that an altered <i>pbp2b</i> gene is required for high-level penicillin resistance.	(103, 104)
High-level resistance to extended spectrum cephalosporins (e.g. cefotaxime)	PBP gene mosaics involving <i>pbp1a</i> and <i>pbp2</i>	Transformation which can happen by a single transformation event.	All known clinical isolates have mosaic forms of <i>pbp1a</i> and <i>pbp2x</i> . PBP2B is not a target for extended-spectrum cephalosporins.	(105)
Intermediate and high-level trimethoprim/sulfamethoxazole resistance	Dihydrofolate reductase (<i>dhf</i>) gene mosaics and/or point mutant alleles	Transformation or spontaneous mutation.	Both mechanisms appear common. <i>dhf</i> mosaics are possibly more frequently observed than simple point mutations involving 3 or fewer bases.	(106, 107, 108)
Intermediate erythromycin resistance	<i>mefE</i> , efflux mechanism	Unknown, probably originated through transformation or conjugative transfer from another species, since <i>mefE</i> is not found in sensitive strains.	Common	(109)
High-level erythromycin resistance	<i>ermAM</i> gene	Conjugative transfer of transposons, including Tn1545 and Tn1545 deletion derivatives, and Tn3872.	Common	(110)
High-level tetracycline resistance	- <i>tetM</i>	Conjugative transfer of Tn1545 and its derivatives and Tn5253	Majority of tetR isolates	(111)
	- <i>tetO</i>	Unknown, probably transformation or transposition	Less common	(112)
High-level chloramphenicol resistance	<i>cat</i> gene	Conjugative transfer of Tn5253, common	Common	(111)
Low-level fluoroquinolone resistance	<i>parC</i> mutations	Transformation, point mutations	Up to 3% resistance of 1997 systemic isolates	(108, 113)
High-level fluoroquinolone resistance	<i>parC</i> and <i>gyrA</i> double mutants	Transformation, point mutations	Up to 1% of 1997 systemic isolates	(108)
Vancomycin tolerance	<i>vncS</i>	Newly-recognized, details not currently known	Identified only in some serotype 9V isolates	(114)

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2. Factors contributing to the spread of resistance

Biological

The genetic basis of resistance in *S. pneumoniae* strongly influences the population dynamics of drug-resistant strains. In contrast to a majority of bacterial species, antimicrobial resistance in pneumococci has not been associated with plasmid carriage. Moreover, resistance due to single-point mutations alone is extremely rare in pneumococcal clinical isolates. Transformation is the most common mode of acquisition of resistance genes, and

resistance determinants spread on conjugative transposons are also common (Table 3). Both of these mechanisms depend on the presence of resistance genes in closely related species, and the presence of free DNA in the environment in the case of transformation, or the opportunity for donor/recipient cellular contact between a donor with a conjugative transposon conferring resistance and a susceptible *S. pneumoniae* recipient for the case of conjugative transposons. Transformation requires homologous recombination following the uptake of resistance determinants, whereas resistance determinants on conjugative transposons can

be inserted into the chromosome in the absence of DNA homology.

Because of these requirements, the rate of acquisition of resistance via these mechanisms may be lower than that associated with resistance due to point mutations. In an environment where neighbouring bacterial strains are not already resistant, there is no potential for sensitive pneumococcal strains to acquire resistance by transformation. Consequently, resistant pneumococcal infections result primarily from the acquisition of resistant pneumococci from the community rather than from the development of resistance during the course of an infection. Moreover, the spread of resistant pneumococcal strains is primarily by clonal amplification rather than repeated independent *de novo* origin.

Additionally, in contrast to pathogens that are associated uniquely with acute infections, *S. pneumoniae* is commonly carried asymptotically in the nasopharynx. Thus, resistant bacteria have a reservoir in healthy people in the community.

Finally, the association between resistance and serotype may play a role in the spread of resistance to the extent that some serotypes may have a higher rate of transmission in the population and a higher probability of causing invasive disease. In addition, the impact of conjugate vaccines on resistance may be modified if non-vaccine serotypes acquire resistance or if resistant vaccine serotypes undergo capsular switching (Section E).

Therapeutic

A large number of studies, both at the community and individual levels, have demonstrated an association between recent therapy with antibiotics and the spread of resistant pneumococci.

Studies at the community level. There is evidence from several countries that increased consumption of some antibiotics, such as β -lactams, correlates with a rise in the prevalence of resistant pneumococcal strains (55, 56, 57). For example, a cross-sectional study of antimicrobial consumption and the carriage rate of penicillin-resistant pneumococci in children in five different communities in Iceland found that children in communities with higher levels of antimicrobial consumption were at higher risk for nasopharyngeal carriage of resistant pneumococci (56). Similarly, a longitudinal analysis of sentinel surveillance for invasive *S. pneumoniae* in the United States found that increases in the

prevalence of penicillin-resistant pneumococci in the early 1990s correlated with increased prescription rates for certain β -lactam agents, while a fairly constant prevalence of tetracycline-resistant pneumococci was associated with slight decreases in the prescription rate for tetracycline (58). Additionally, some studies have shown that declines in antibiotic use at the community level correlate with declines in the prevalence of resistant streptococci. The prevalence of penicillin-resistant pneumococci in Hungary (59) and in Iceland (60) declined following reduced antimicrobial use. Few studies, however, have collected longitudinal data on both the prevalence of resistant strains and the volume of drug use in order to establish a direct link between declines in drug consumption and the prevalence of resistance.

However, the prevalence of resistance need not always be proportional to the rate of antibiotic usage. For example, if resistant strains do not have a fitness disadvantage over sensitive strains in the absence of antibiotics they can be expected to persist even if antibiotic usage is reduced or eliminated (61, 62). Since penicillin-binding proteins (PBPs) are essential cell wall synthesis enzymes, it seems logical that alterations in these enzymes associated with a β -lactam-resistant phenotype might result in growth deficiencies. In fact, resistant clinical isolates with PBP alterations also often have dramatically altered peptidoglycan structure. These mutants are not only β -lactam-resistant, but unaffected in general physiology as well, and thus able to persist in the absence of direct antibiotic selection.

Studies at the individual level. A number of cross-sectional studies have identified recent antimicrobial use by individuals as a risk factor for carriage of resistant pneumococci by those same individuals. This association has been observed in populations with high (15, 63) and more moderate prevalences of pneumococcal nasopharyngeal carriage (64). For example, in the Iceland study by Arason et al., children with recent antimicrobial use (within the last 7 weeks) were at higher risk for carriage of penicillin-resistant pneumococci (57); similarly in a day-care centre in Israel where the prevalence of carriage in children was greater than 60%, and resistance to at least one drug was greater than 50%, exposure to antimicrobial therapy in the previous month was significantly associated with the likelihood of carrying resistant pneumococci in a multivariate analysis (65). In contrast, antibiotic use in the more distant past (3 months ago or longer) typically has not been associated with a

greater risk of resistant nasopharyngeal carriage (66). Additional factors that cross-sectional studies have often identified as risk factors for resistant pneumococcal carriage include young age (with highest carriage often in individuals <1 year old) and attendance at day-care centres.

Studies have also shown correlations between recent antibiotic use and the incidence of invasive disease caused by non-susceptible pneumococci (64). This suggests that recent antimicrobial use not only increases the risk that an individual will carry, and therefore potentially transmit resistant pneumococci, but that it also increases the risk that the individual will develop invasive pneumococcal illness caused by resistant pneumococci.

Studies investigating the effect of antibiotic use on the nasopharyngeal flora within individuals are less common although they contribute importantly to understanding how antibiotic use leads to increased resistance. Longitudinal studies of individuals have shown an increase in the relative proportion of resistant pneumococci among carriers following both prophylactic antimicrobial treatment (67, 68) and treatment of acute pneumococcal infections (69). This results primarily from a decrease in the carriage of susceptible pneumococci, and thus is not necessarily associated with an overall increase in the prevalence of resistance in the study population.

Non-human use

While antimicrobial use in agriculture and farming poses a concern for a number of enteric pathogens, non-human use of antibiotics is not of direct concern for the case of pneumococci because it is strictly a human pathogen and plasmid-borne resistance does not play a key role.

Commercial/economic factors

In developing countries, commercial and economic factors determine which antibiotics are available. Typically amoxicillin and co-trimoxazole are among the most affordable, and thus the most commonly used antibiotics for respiratory infections.

3. Summary: Causes of resistance

- Transformation, the uptake of free DNA from closely related bacterial strains or species, and conjugative transposons carrying resistance genes, are the key genetic mechanisms conferring pneumococcal resistance. Point mutation

plays only a small role, in contrast to other pathogens such as HIV and mycobacteria, where resistance also poses problem.

- Therapeutic factors play a key role in the spread of resistance. Increased use of antimicrobials is associated with an increase in the prevalence of pneumococcal resistance at the community level. At the individual level, recent antibiotic use is associated with an increased risk of carrying resistant pneumococci, and of acquiring invasive disease caused by resistant pneumococci.

4. Research needs: Causes of resistance

- Further investigation of the mechanisms resulting in the association between recent antibiotic use and carriage of resistant *S. pneumoniae*.** The biological mechanisms resulting in the association between recent antibiotic use and carriage of resistant *S. pneumoniae* have not been well studied. Possible mechanisms fall into three broad categories: the unmasking of a resistant pneumococcal clone that was present at a low density in the nasopharynx prior to antimicrobial therapy; replacement of sensitive pneumococci with resistant pneumococci acquired from the community during or after antimicrobial therapy; and within-host evolution of a resistant pneumococcal population in response to the selective pressure of antimicrobial therapy. Distinguishing features of these alternative mechanisms are discussed in more detail in Table 4.

A better understanding of which of these mechanisms generate the observed association would provide an important framework for developing interventions to prevent the spread of resistance. For example, if replacement of sensitive strains with resistant strains from the community is the primary mechanism, then antibiotics which clear the nasopharynx may increase the risk of resistant carriage more than antibiotics which do not. In contrast, if unmasking is the primary mechanism then antibiotics which clear the nasopharynx of both sensitive and resistant strains may be the most effective treatment. Optimal treatment is likely to vary with the prevalence of resistant strains in the community, which influences both the risk of multiple carriage and of acquiring resistant strains during and after treatment. Longitudinal studies of nasopharyngeal carriage before and

TABLE 4. HYPOTHESES FOR THE MECHANISMS GENERATING THE ASSOCIATION BETWEEN RECENT ANTIMICROBIAL THERAPY AND NASOPHARYNGEAL (NP) CARRIAGE OF RESISTANT PNEUMOCOCCI, AND DISTINGUISHING PREDICTIONS OF EACH HYPOTHESIS*

Hypothesis	Predictions		
	Pre-treatment	During treatment	Post-treatment
Unmasking: Antibiotic therapy leads to the amplification of minority resistant clones that colonized the NP prior to treatment	The NP flora consists of a majority sensitive population and a minority population resistant to the prescribed antibiotic	The minority population increases and the majority population decreases	The majority population is genetically identical to the pre-treatment minority population
Replacement during therapy: Colonization by a resistant strain from the community occurs during antibiotic therapy	The NP flora is sensitive to the prescribed antibiotic; a minority resistant population may or may not be present	The sensitive population declines; a genetically-distinct strain appears; this strain is resistant to the prescribed antibiotic	The newly-acquired resistant strain dominates; pre-treatment strains are in the minority, or not detectable
Replacement after therapy: Antibiotic therapy reduces the NP flora sufficiently to increase the likelihood of recolonization post-antibiotic therapy	The NP flora is sensitive to the prescribed antibiotic; a minority resistant population may or may not be present	The majority population declines until carriage reaches low levels or is eradicated	NP flora returns to high levels; the majority strain may be sensitive, resistant to the antibiotic used for therapy, or resistant to other antimicrobials, depending on the prevalence of resistant strains in the community
Within-host evolution of resistance: Antibiotic-mediated selection results in amplification of a resistant mutant arising either by point mutation or transformation before or during treatment	The NP flora is sensitive to the prescribed antibiotic; a minority resistant clone is not detectable	The sensitive population declines; a resistant population appears and increases; the resistant population is of the same serotype as the sensitive population	A resistant strain dominates; this strain is genetically identical to the dominant pre-treatment strain, except at the loci associated with resistance

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after the initiation of antibiotic treatment provide data that can distinguish among alternative mechanisms for the increased risk of carrying resistant pneumococci following antimicrobial treatment (Table 4).

- b. **Further investigation of the association between resistance and serotype.** Why some serotypes are not associated with resistance becomes a question of particular importance as the pneumococcal conjugate vaccine is introduced.
- c. **How frequent and important is capsular switching?** This genetic event has only been documented recently, and it is still unclear how

commonly it occurs. Because both resistance and transmissibility have an association with pneumococcal serotype, frequent capsular switching could have an impact on the spread of resistance within communities. Moreover, because interventions such as the pneumococcal polysaccharide and conjugate vaccine (discussed in section E) are both designed to confer protection against the most common pneumococcal serotypes, capsular switching could decrease the efficacy of these interventions. In particular, because the conjugate vaccine appears to protect against pneumococci of vaccine-associated serotypes, mass vaccination may result in strong selection for capsular switching.

C. Detection of resistance

1. Laboratory-based methods

Basic equipment required for bacterial isolation and antimicrobial resistance testing includes: autoclave, refrigerator, freezer, Bunsen burner, microscope (100X), hand lens, centrifuge, balance. Additional supplies (media and equipment) are summarized in a WHO manual for the national surveillance of antimicrobial resistance of *S. pneumoniae* and *H. influenzae* (71).

Salient features of standard laboratory tests for detecting resistance are summarized in Table 5. Both the agar and broth microdilution tests are considered “gold-standard” methods for estimating the MIC of a particular antimicrobial agent. Antimicrobial agents are typically tested at twofold serial dilutions and the lowest concentration that inhibits bacterial growth is the MIC. MICs estimated by these tests are highly accurate and repeatable. While both methods of MIC-testing do not require additional equipment from that needed for bacterial isolation, they require technical expertise and additional reagents. Moreover, they are both labour-

intensive and time-consuming to prepare (70).

The disk-diffusion method is a simpler method which involves placing filter-paper disks impregnated with specific concentrations of antimicrobial agents on an agar plate inoculated with the test organism. The size of the zone of inhibition around the disk is inversely related to the MIC but, because this method depends on the rate of diffusion of the agent through the agar and on the rate of growth of the bacteria being tested, this method cannot be used to estimate MICs directly (70). Instead, categorization of organisms as sensitive or resistant to a few agents is possible based on known breakpoints. This test is technically simple, does not require specialized equipment and is not labour-intensive to perform. However, it only yields a qualitative result which is not always adequate for characterization of β -lactam resistance in pneumococci (71).

The E-test is a newer, simplified method of quantitative antimicrobial susceptibility testing. A pre-formed antimicrobial gradient on a plastic strip is

TABLE 5. ADVANTAGES AND DISADVANTAGES OF DIFFERENT LABORATORY METHODS OF PNEUMOCOCCAL SUSCEPTIBILITY TESTING

	Agar microdilution	Broth microdilution	E-test	Disk diffusion
Accuracy	Well-standardized repeatable	Well-standardized repeatable	High agreement with microdilution methods (69)	Qualitative test; does not estimate MIC
Cost	Moderate	Moderate	Expensive	Cheap
Timeliness	Time-consuming to prepare	Time-consuming to prepare	16-20h incubation	16-18h incubation
Technical skills and equipment required	Moderate	Moderate	Low	Low
Source of sample	Requires pneumococcal isolate	Requires pneumococcal isolate	Requires pneumococcal isolate	Requires pneumococcal isolate
Sustainability of reagents	Antibiotic solutions lose viability; reagents cannot be prepared too far in advance	Antibiotic solutions lose viability; reagents cannot be prepared too far in advance	Strips can be stored refrigerated for long periods of time	Disks can be stored refrigerated for long periods of time
Use for treatment of individuals*	Good	Good	Good	Moderate
Use for monitoring resistance	Good	Good	Good	Only allows for a crude monitoring of trends

* Most treatment of pneumococcal disease is empiric; moreover resistance has only been shown to have a clinical impact for particular syndromes (see Section A). Thus, susceptibility-testing to guide treatment is of use only in limited cases.

allowed to diffuse onto an agar plate inoculated with the test organism. Several strips with different agents can be placed on a single plate. The MIC is read as the concentration of antibiotic at the point where the zone of inhibition intersects with the strip. This test combines the simplicity of disk-diffusion with the quantitative results of dilution methods. However, the pre-formed plastic strips are significantly more expensive than the reagents necessary for the above methods.

Rapid methods for detecting β -lactam and sulfamethoxazole resistance

Currently, isolating pneumococci from clinical specimens and determining penicillin susceptibility takes 2–3 days. Assessment of β -lactam or trimethoprim resistance can also be obtained by DNA sequence analysis of resistance gene amplicons. Such analysis is faster than culture-based approaches and has a low probability of generating artefactual results. Newer, fingerprinting and nested PCR approaches have the potential to allow for pneumococcal identification and susceptibility testing within a few hours.

All of these tests require an extremely high level of technical expertise and highly-specialized PCR and sequencing equipment as well as high-quality laboratory facilities. These methods are currently still under development and are not standardized or routinely performed. They are not at this point feasible for the vast majority of developing countries although specialized laboratories are beginning to utilize these techniques.

2. Clinic-based methods

Currently there are no clinic-based methods for identification of pneumococcal resistance. Pneumococcal isolation is required and this must be performed in a laboratory. A urine antigen test is currently under development. The utility of such a test at this point remains unclear; it appears to detect pneumococcal carriage as well as infection and thus is unlikely to be a useful diagnostic tool, particularly for children where pneumococcal carriage is common. Additionally, because an isolate is not obtained, this test does not allow for serotype or resistance testing.

3. Summary: Detection of resistance

- Methods of detecting pneumococcal resistance appropriate for developing country laboratories are summarized in a WHO manual for the national surveillance of antimicrobial resistance of *S. pneumoniae* and *H. influenzae*. The gold standards are broth and agar microdilution.
- All methods require isolation of a pure bacterial culture, followed by susceptibility testing, and take at least 3 days to complete.
- There are no clinic-based tests that can be performed to assess resistance.

4. Research needs: Detection of resistance

More research into rapid, inexpensive methods for detecting resistance is necessary. The E-test offers a promising alternative to broth and agar microdilution but currently remains more expensive than most developing countries can afford. It may be possible to determine meaningful cut-offs for the disk diffusion method that can serve as a surrogate for quantitative MIC testing.

D. Treatment

1. Standard treatment guidelines for disease management

As part of IMCI, WHO developed guidelines for the management of ARI that rely on detection of cases based on simple clinical signs (25). Recommended outpatient antibiotic therapy includes either co-trimoxazole bid, for 5 days (children <1 yr should receive 1/2 adult tablet per dose; children 1–5 years should receive 1 adult tablet) or amoxicillin, tid for 5 days (approximately 40 mg/kg/day). For ear problems, WHO guidelines recommend the following: patients with mastoiditis should be given an immediate dose of antibiotics and be referred to a hospital for further treatment; children with acute ear infections should be prescribed a 5-day course of antibiotics; those with chronic ear problems should not be given antibiotic therapy but should be followed. Similarly, patients with serious pneumonia should be hospitalized and given a dose of antibiotics immediately. Less severe pneumonia should be treated with a 5-day course of antibiotics. Patients with coughs and colds should not be given antibiotic therapy. Meningitis patients require immediate hospitalization and antibiotics. Children with any clinical signs and severe malnutrition are also categorized in the severe disease category. While the threshold for prescribing antibiotic therapy for respiratory infection in children with severe malnutrition or immunosuppression may be lower, it is equally important in these children to use antibiotics prudently because resistant infections pose an even greater threat to these children.

The WHO guidelines are not intended for industrialized countries. Most of these countries do not have unified guidelines for the treatment of pneumococcal disease, although professional societies, for example the American Thoracic Society (72) and the Infectious Diseases Society of America (73), have published recommendations for the treatment of community-acquired pneumonia in adults. In the recommendations from these two societies, first-line agents for outpatient therapy include macrolides and tetracycline.

In response to the emergence of antibiotic-resistant pneumococci, practitioners in industrialized countries are starting to revise management strategies for pneumococcal infections.

Kaplan and Mason (45) review a number of proposed modifications for the treatment of meningitis, bacteraemia, pneumonia, and upper respiratory infections caused by resistant pneumococci. A recent report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group recommends oral amoxicillin as the first-line antibiotic for the treatment of acute otitis media, but recommends increasing the standard dosage to 80–90 mg/kg/day (51).

2. Definition of cure: no pathogens or no symptoms?

Clinical outcome is typically the primary outcome of concern for pneumococcal infections. However, bacterial eradication is more sensitive in differentiating effective from ineffective treatments. Eradication of the pathogen can be difficult, but a recent study showed that successful early bacterial eradication in children with acute otitis media resulted in a better clinical outcome (74). Additionally, bacteriological outcome often can only be measured by an invasive procedure, for example blood culture or tympanocentesis. Moreover, because pneumococcus is normally carried as a commensal in the nasopharynx, eradication of carriage is not a feasible outcome.

3. Data to support the efficacy of treatment guidelines to cure and the impact of treatment guidelines on resistance at the individual and population level

Efficacy of treatment guidelines

A number of studies have assessed the effectiveness of the WHO ARI-management strategy at improving childhood survival. A review of six published studies assessing pneumonia case-management found that infant mortality was reduced by 15.9 deaths per 1000 live births and that mortality

among children <5 years of age was reduced by 36 deaths/1000 live births (2). A controlled intervention trial among children under 5 years in Nepal found that subdistricts that were served by health care workers using the WHO strategy had a 28% reduction in the risk of death from all causes by the third year of implementation (75). The greatest risk reduction was in infants and deaths due to other conditions such as diarrhoea and measles also declined. A similar targeted ARI programme in rural Bangladesh led to a 28% decline in ARI mortality in the intervention area; the combination of ARI-targeted programmes with non-ARI specific interventions reduced overall mortality by as much as 50% (76).

Efficacy of treatment guidelines to limit resistance

Programmes to encourage judicious antibiotic use are the only treatment guidelines that have been evaluated for their impact on pneumococcal resistance. Countrywide initiatives to reduce antibiotic resistance by reducing antibiotic use were attempted in Finland for the case of macrolide-resistant group A streptococci (GAS), and in Iceland for the case of penicillin-resistant *S. pneumoniae*. GAS has some features in common with *S. pneumoniae* including the genetic mechanism of erythromycin resistance and a carriage state. In Finland, in response to a dramatic rise in the prevalence of erythromycin-resistant GAS from 5% in 1988–1989 to 13% in 1990, national guidelines recommending reductions in the outpatient use of macrolide antibiotics were issued in 1991. Total macrolide consumption in outpatient therapy declined from 2.4 daily doses per 1000 inhabitants in 1991 to a level of 1.38 in 1992; the daily doses per 1000 inhabitants remained between 1.28 and 1.74 during the next 5 years (77). From 1992 to 1996 the prevalence of erythromycin-resistant GAS isolates also decreased from 16.5% in 1992 to 8.6% in 1996. This decline was evident after 1993, approximately two years after the release of national guidelines. Thus, a reduction in antibiotic use was associated with a subsequent decline in the prevalence of resistant GAS strains although a causal link cannot be established because of the observational study design. However, although the prevalence of resistant GAS declined, it remained at close to 9%; moreover an apparent increase in the consumption of azithromycin and roxithromycin that correlated with declines in erythromycin use may reflect a shift, rather than a sustained reduction in macrolide use.

In Iceland, the incidence of penicillin-resistant pneumococci among patients with invasive pneumococcal disease increased from 0% in 1988 to 16.3% in 1992 (78). A majority of penicillin-resistant strains were also resistant to macrolide antibiotics and to trimethoprim/sulfamethoxazole. The country responded to this rapid increase in resistant pneumococci by launching a public health campaign against the overuse of antibiotics that was aimed both at the public and at physicians. Additionally, children undergoing antibiotic therapy, and known carriers of non-susceptible pneumococci with colds or coughs were discouraged from going to day-care centres. The number of daily doses of antibiotics in Iceland decreased from 23.6/1000 inhabitants in 1990 to 21.4 in 1994, due largely to decreased use of macrolides and trimethoprim/sulfamethoxazole (78). The incidence of penicillin-resistant invasive pneumococcal isolates declined from a peak of 19.8% in 1993 to 18.6% in 1994; among pneumococcal carriers, the proportion of healthy children attending day care that were colonized by a resistant strain decreased from 20% in 1992 to 16% in 1995 (78). These data are also suggestive of a decline particularly within the context of rapid rise in resistance in Iceland in previous years.

Two recent controlled studies assessed the impact of well-defined judicious antibiotic use interventions on antibiotic prescribing practices and the incidence of resistant pneumococcal strains. The impact on antibiotic prescription rates of an intervention targeting four adult primary care practices in Denver, Colorado, United States was evaluated using a prospective, non-randomized controlled trial design (79). The intervention, which was aimed at reducing antibiotic prescribing for outpatient adults diagnosed with uncomplicated acute bronchitis, consisted of household and office-based patient educational materials, and clinician education, practice profiling and academic detailing. During the one-year study period, practices which received the full intervention showed a significant decline in antibiotic prescription rates, from 74% to 48%, whereas no significant decline was detected for control sites (79). Practices which received only a limited intervention, which consisted solely of office-based educational materials, also did not show significant declines. While this study did not address the impact of reduced prescription rates on the incidence of resistant pneumococci, it does suggest that active education of clinicians about the importance of judicious antibiotic use can lead to

reduced rates of antibiotic prescription.

An evaluation of judicious antibiotic use interventions in Alaskan villages (80) was designed to evaluate both antibiotic prescribing rates and the prevalence of non-susceptible pneumococci in villages receiving the intervention and in control villages. The intervention focused on otitis media and consisted of an educational programme for village health aides and their consultants, workshops on the appropriate diagnosis of otitis media, and information sheets to providers, and village residents. Respiratory health care visits for children <5 years decreased by 23% and antimicrobial prescriptions per respiratory visit decreased by 22% in the intervention region while no declines were evident in control villages which did not receive the intervention (81). Additionally, although the overall prevalence of pneumococcal carriers did not decrease in the intervention area, the proportion of all pneumococcal isolates that were non-susceptible to penicillin (MIC \leq 0.1 mg/ml) declined by 28% in the intervention region, but did not decline significantly in the control regions (81).

Thus, studies from the village to country levels demonstrate that judicious antibiotic use interventions can result in reduced antibiotic prescriptions. Evidence that such interventions also lead to decreases in pneumococcal resistance is less strong. Declines in penicillin-resistant pneumococci in Iceland, and in Alaskan villages receiving interventions suggest that judicious use campaigns may have the potential to limit the spread of resistant pneumococci. Controlled studies of interventions designed to look at the prevalence of resistant pneumococci as an outcome are needed to further address the effectiveness of this class of interventions.

4. Data showing relationship between emergence of resistance and drug quality, misdiagnosis, use of a related drug for another disease, suboptimal regimens, use of drugs in humans and animals

The key factor influencing the emergence of resistant pneumococci is unnecessary antibiotic use for viral respiratory infections in humans. This is due in part to misdiagnosis of conditions because both viral and bacterial agents can cause clinical syndromes associated with pneumococcal infection, and community-acquired pneumonia, otitis media and acute respiratory infections are typically treated empirically. It is also due to overuse of antibiotics in humans because of a variety of factors includ-

ing: lack of awareness among physicians of the association between increased antibiotic use and the increased risk of resistant disease in their individual patients; pressure from patients for a rapid cure for their illness; and the speed and simplicity of prescribing an antibiotic rather than explaining to a patient why one is not necessary. In some developing countries antibiotics are available without prescriptions and this potentially facilitates overuse, although the expense of antibiotics often deters indiscriminate use of antibiotics in these settings. We note, however, that while unnecessary antibiotic use is a problem in some cases, in developing countries where access to health care is difficult a number of children requiring antibiotic therapy do not have the opportunity or resources to receive it. Thus while inappropriate antibiotic use is a key problem contributing to resistance, the issues are not exactly analogous to those in the developing world.

The use of similar drugs for unrelated conditions also contributes to the problems of resistance. For example, widespread use of sulfadoxine/pyrimethamine as a treatment for malaria leads to an increased risk of carrying co-trimoxazole-resistant pneumococci (82). It is also possible that widespread use of co-trimoxazole to treat respiratory infections contributes to Fansidar-resistant *Plasmodium* in malaria-endemic regions.

Mass chemoprophylaxis campaigns to prevent conditions such as trachoma and sexually-transmitted diseases also have the potential to increase the burden of pneumococcal resistance in a number of developing countries where resistance does not currently pose a serious public health threat. A recent initiative in a number of African countries to eradicate trachoma using mass azithromycin prophylaxis may lead to increases in resistant pneumococci. A study of the impact of mass prophylaxis in an aboriginal village in Australia found that macrolide resistance increased from very low levels (1%) to as high as 21% of isolates 2 months after treatment, and persisted above the baseline level for the entire 6-month observation period (67). While macrolides are not commonly used to treat respiratory infections in developing countries because of their high cost, macrolide resistance in pneumococci is often associated with resistance to other more commonly used antibiotics such as amoxicillin and co-trimoxazole. The biological basis of this association, which has been observed repeatedly, is not fully understood and may be driven in part by the association between serotype and resistance profiles. If

mass chemoprophylaxis against trachoma results in an increase in the prevalence of pneumococci that are resistant to β -lactams and co-trimoxazole, this would pose a serious threat to the effective treatment of acute respiratory infections in these countries, and would also increase the potential for such strains to spread to regions where trachoma control programmes are not implemented.

Other factors such as reduced drug quality and suboptimal regimens may also play a role in the emergence of pneumococcal resistance. Suboptimal and long-duration regimens increase the opportunity for acquisition and/or amplification of resistant *S. pneumoniae*. The importance of these factors is difficult to determine, but is likely to play a smaller role than inappropriate use of antibiotics (e.g. use of antibiotics for viral respiratory infections). Use of similar antibiotics in animals is not an issue of central concern for pneumococci, because animals are not a reservoir for this bacteria and plasmid-borne resistance is rare relative to that conferred by transformation and conjugative transposons.

5. Strategies for improving treatment and evidence that these will contain spread

Because the primary genetic mechanism of resistance in pneumococci is transformation as opposed to point mutation, resistance is thought to arise *de novo* only rarely in individuals. Interventions to contain the spread of resistance in pneumococci thus differ in important ways from those used for pathogens where resistance typically evolves from initially sensitive pathogen populations in response to antibiotic-mediated selective pressure (Table 6).

One potential area for intervention is modification of standard antibiotic treatment regimens. Recent evidence suggests that shorter treatment courses are sometimes clinically as effective as standard treatments. Shorter-course therapies are easier for patients to complete with a high level of compliance. Observational studies have also suggested that short-course, high-dose therapy may reduce the risk that individuals carry resistant pneumococci after antibiotic therapy (83). Simple modifications of treatment regimens represent a feasible, low-cost intervention to limit the spread of resistance in developing countries.

6. Ethical issues: benefits to individual vs. benefits to community

Judicious antibiotic use has the potential to benefit individuals as well as the community. At the community-level, the incidence of antibiotic use correlates with the prevalence of resistance. Moreover, communities which have implemented policies to reduce antibiotic use have often experienced declines in the prevalence of resistant pathogens (57, 77). Benefits to the community are likely long term since the time scale for declines can be slow. For the case of individuals, recent antibiotic use is associated with an increased risk that individuals carry resistant pneumococci after treatment. Thus individuals who use antibiotics judiciously are at a reduced risk of carrying resistant pneumococci compared to those that take them indiscriminately. They are also at a reduced risk of developing invasive disease caused by a resistant strain. This benefit is short term, since the average duration of pneumococcal carriage is 2–3 months.

7. Drug policy strategies and the data on which they are based: switch, rotation, reservation, combination drugs

The strategies of drug switching and drug cycling were developed primarily in the context of nosocomially-acquired infections, such as those caused by vancomycin-resistant enterococci or methicillin-resistant *Staphylococcus aureus*. In contrast, the vast majority of pneumococcal infections are community acquired, and the implementation of drug cycling at a community level is not straightforward. Moreover, the success of drug cycling at reducing the spread of resistance remains controversial even in the nosocomial setting. Combination therapy for pneumococcal disease is used in some cases to increase clinical efficacy, but has not been used as a method of preventing resistance. Because within-host evolution of resistant pneumococci by point mutation is extremely rare, it is not clear whether combination therapy represents an effective intervention, as it does in the case of tuberculosis and HIV (Table 6).

8. Summary: Treatment

- The WHO algorithm for the treatment of ARI as part of the IMCI programme is the recommended method of managing pneumococcal disease among children in developing countries.

TABLE 6. PRINCIPLES OF PREVENTING THE DEVELOPMENT AND TRANSMISSION OF RESISTANCE DUE TO ANTIMICROBIAL THERAPY*

	Pathogens where a carrier state is uncommon**	Pathogens with a carrier state
Examples of pathogens	<i>Plasmodium falciparum</i> , <i>Shigella</i> , <i>Mycobacterium tuberculosis</i>	<i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , group A streptococci
Overall goal	To prevent the development of resistance during treatment	To prevent the acquisition or amplification of resistant strains at the site of carriage during treatment
Method 1: Avoid unnecessary antibiotics (e.g. for viral infections)	Minor concern	Major concern
Method 2: Modify treatment duration	Longer-course treatment is preferred over short course to ensure the pathogen has been eradicated. Failure to eradicate the pathogen results in clinical treatment failure	Short-course therapy may be advantageous because the time period during which an individual may acquire a resistant strain is reduced. Eradication of the pathogen from the site of carriage is not a practical therapeutic goal
Method 3: Use high dosages	Rationale: High dosages can eradicate both intermediate and high-level resistant pathogens facilitating pathogen eradication and reducing the opportunity for resistant mutants to proliferate	Impact on bacterial carriage unknown. Eradication of pathogen from the site of carriage is not a practical therapeutic goal, even for high dose therapy
Method 4: Treat with drugs that minimize the selection for resistance	Likely to have only a minor impact; drugs which do not exert a strong selective pressure are typically less efficient at eradicating the pathogen	Likely to have only a minor impact. May reduce the probability of unmasking of minority resistant strains or acquisition of resistant strains from the community
Method 5: Treat with multiple drugs	Rationale: Resistance is often due to point mutations, insertions, deletions. The likelihood of a single genetic event conferring resistance to multiple drugs is the product of the separate likelihoods	Impact unknown. May not be effective for pneumococci, since <i>de novo</i> resistance due to point mutations, insertions and deletions alone is rare
Method 6: Cycling of drugs	Impact unclear; may be useful for hospital-acquired infections	Unlikely to be effective because the majority of infections are community-acquired, and because the pathogens are often exposed to drugs used for the treatment of unrelated conditions
Method 7: Encourage adherence to treatment regimen	Erratic treatment allows pathogen to proliferate at sub-therapeutic MICs, increasing the opportunity for resistant mutants to amplify	Unclear whether poor compliance increases or decreases the risk of carrying resistant pneumococci

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** Carrier state refers to cases where pathogen populations are commonly present asymptotically in the nasopharynx, vaginal or intestinal tract, and where such asymptomatic populations serve as primary reservoirs for disease transmission. While diseases such as HIV and TB have latent periods, these periods are associated with low levels of pathogen replication and are thus not associated with high risk of acquiring resistance or transmitting the disease.

- The goal of treatment is clinical cure; bacteriological cure is often a better outcome for clinical efficacy trials.
- Inappropriate use of antibiotics is a key factor driving pneumococcal resistance. Overuse for viral respiratory infections contributes to resistance; this is common in industrialized countries and in some developing settings. Interventions encouraging judicious antibiotic use can address this problem, and have had some impact in industrialized countries. In some developing settings, however, limited access to health care still prevents children from receiving antibiotics when they are necessary, and judicious antibiotic use campaigns have not been a high public health priority.
- Use of closely related drugs for other conditions also plays a role in the spread of resistance.
- Use of Fansidar to treat malaria can lead to an increase in co-trimoxazole-resistant pneumococci.
- Mass antibiotic chemoprophylaxis for conditions such as trachoma and sexually-transmitted diseases also has the potential to increase resistance in respiratory pathogens.
- Alterations of antibiotic dose and duration of treatment that maintain clinical efficacy may decrease an individual's risk of acquiring resistant pneumococci post treatment

9. Research needs: Treatment

1. Study the effect on pneumococcal resistance of drugs used for other conditions
 - a. The impact of co-trimoxazole use on Fansidar resistance.
 - b. The impact of mass azithromycin prophylaxis on respiratory pathogen resistance.
2. Study the impact of dose and duration of treatment on the risk of carrying resistant pneumococci post treatment.
3. Evaluate the effectiveness of the WHO algorithm for managing adult ARI.
4. Assess the impact of antibiotic control programmes on pneumococcal resistance.

E. Prevention of pneumococcal disease

1. Known interventions

Pneumococcal polysaccharide vaccine

A polysaccharide vaccine is currently available which can protect individuals >2 years of age against invasive pneumococcal infections caused by common *S. pneumoniae* serotypes. The efficacy of this vaccine varies depending on a person's age and immune status; in case-control studies the effectiveness of the vaccine against invasive disease has ranged from 56% to 81% (84). Strongest recommendations for vaccination are for people over 65 years of age, and people aged 2–64 years with the following risk factors: chronic cardiovascular disease, chronic pulmonary disease, diabetes mellitus, or functional asplenia (84).

The polysaccharide vaccine has the following limitations: it does not induce an effective immune response in children less than 2 years old, an age group with a high burden of disease in developing countries; it does not protect against non-bacteraemic pneumococcal disease or common upper respiratory diseases (e.g. acute otitis media, sinusitis); it does not protect against carriage of pneumococci; declining antibody levels following vaccination suggest that vaccine-induced immunity may wane over a 5–10 year period.

The fact that the vaccine is not indicated for children <2 years of age and is primarily recommended for the elderly prevents it from being an effective intervention against pneumococcal disease in most developing country settings.

2. Interventions currently undergoing testing

Pneumococcal conjugate vaccine

Pneumococcal conjugate vaccines, where purified polysaccharide of the epidemiologically most important serotypes are conjugated to a carrier protein, are currently undergoing clinical trials. A 7-valent formulation is expected to obtain FDA licensure by the year 2000, and an 11-valent formulation is also undergoing clinical trials. Prelimi-

nary data suggest that these vaccines are appropriate for children <2 years of age. No significant safety problems associated with vaccination have occurred in Phase I-III trials conducted since 1992 (85). Clinical trials show that the vaccine is highly effective at preventing invasive disease due to serotypes included in the vaccine (86, 87). The vaccine also has some efficacy against non-invasive disease (85).

It is likely that the cost of the vaccine will make it unavailable to many developing countries. In addition to preventing invasive pneumococcal disease, however, the conjugate pneumococcal vaccine also has great potential as an “anti-resistance” vaccine. There are also preliminary data suggesting that the pneumococcal conjugate vaccine reduces carriage of vaccine serotypes (88, 89), similar to the conjugate *Haemophilus influenzae* type b vaccine (e.g. (90)). This effect has been demonstrated in infants (89) as well as toddlers (63), and raises the possibility that the conjugate vaccine may be effective at preventing colonization with vaccine-related serotypes, thus reducing the opportunity for transmission of these serotypes within communities. Because the serotypes in current formulations of the vaccine include paediatric serotypes that are commonly associated with antibiotic resistance, vaccination of infants may potentially reduce the circulation of antibiotic-resistant strains (89). Additionally, if the conjugate vaccine is effective at preventing invasive disease in children, and in particular if it reduces the rate of otitis media, antimicrobial therapy for pneumococcal infections is likely to decline, thus reducing the selective pressure for resistance. There is the possibility, however, that the vaccine prevents carriage of vaccine-included serotypes only. Evidence from a vaccine trial in the Gambia (88) and a recent study of day-care attendees in Israel (91) suggest that carriage of non-vaccine serotypes increases following vaccination, although a previous study in Israel did not find evidence of increased carriage of non-vaccine serotypes in toddlers in Israel (92). The impact of mass vaccination on carriage of non-vaccine serotypes remains to be seen, as well as whether

widespread use of the conjugate vaccine increases the selective pressure for serotype switching or the acquisition of antibiotic resistance in strains not covered by the vaccine. Whether widespread use of the conjugate vaccine will increase the selective pressure for serotype switching in the serotypes covered by the conjugate vaccine, and whether the non-vaccine serotypes will be more likely to acquire antibiotic resistance if populations of the common paediatric serotypes decline remain to be seen.

Because of the great potential of the conjugate vaccine to reduce both the burden of disease and resistance, evaluation of the impact of the conjugate vaccine is a top research priority.

Vitamin A

High-dose vitamin A supplements have been shown to reduce morbidity and mortality in children with acute measles infection (93). This, along with evidence that vitamin A plays a role in maintaining mucosal and lymphoid tissues and that reduced vitamin A levels in serum are associated with measles, varicella and respiratory syncytial virus infections (94), has led to the hypothesis that vitamin A supplements may be an effective intervention against ARI in children. A clinical trial testing whether high-dose vitamin A enhanced recovery of children 3 months to 10 years of age hospitalized for community-acquired pneumonia in Peru found that vitamin A was associated with increased rather than decreased clinical severity relative to the placebo group. The role of vitamin A in protecting against severe pneumococcal infections has not been directly investigated, although studies in developing countries have in some cases suggested that vitamin A supplements may protect against severe ARI in children (95, 96). Clinical trials of high-dose vitamin A in children with respiratory syncytial virus infection have failed to find a benefit to supplementation (97) and in one case found a detrimental effect of vitamin A supplementation (98). Consequently, use of high-dose vitamin A as a therapeutic intervention for ARI should be considered with caution in patients without known vitamin A deficiency or concurrent measles infection until further evidence is available.

Xylitol sugar

Xylitol is a sugar that has been used as a sweetening substitute for sucrose because it has a preventive effect against dental caries. Recent evidence suggests that in addition to inhibiting growth of

Streptococcus mutans, the primary cause of dental caries, this sugar can inhibit the growth of *S. pneumoniae*, and possibly also of other bacterial colonizers of the nasopharynx such as *H. influenzae* (99, 100).

A controlled trial of healthy children attending day-care centres in Finland randomized children to control groups which received syrup, chewing gum and lozenges sweetened with sucrose and a low concentration of xylitol, or treatment groups which received a high daily dose of xylitol in the form of syrup, chewing gum or lozenges (99). The children were then followed for a 3-month period and information on respiratory infections, acute otitis media, and antibiotic therapy was collected. While the xylitol exposure did not reduce the mean number of respiratory infections in treatment groups relative to their respective control groups, children who regularly received xylitol in the form of syrup or chewing gum had a significant 30–40% reduction in the occurrence of acute otitis media, and all treatment groups received fewer antibiotic prescriptions than controls (99). Prophylactic use of xylitol may thus protect against acute otitis media, particularly for children with high exposure to *S. pneumoniae*, such as those attending day-care centres. In this study, xylitol in all groups was administered 5 times per day; such frequent dosing may be difficult to achieve and studies of the minimum dosing required to get a significant protective effect would be useful. Xylitol syrup or chewing gum may be a feasible prophylactic measure in some developing settings, with the potential of reducing antibiotic use.

Additional interventions

Indoor air pollution: Exposure to cigarette smoke and to smoke from some woodburning stoves has been identified as risk factors for invasive pneumococcal disease. Thus, limiting exposure to smoke may help reduce the pneumococcal disease burden in children. Because pneumococcal disease is not waterborne, and because the primary reservoir is the human nasopharynx, interventions to improve water quality and environmental sanitation are not likely to have any impact on pneumococcal disease. Educational campaigns to increase hand washing may have a small impact on limiting transmission.

3. Summary: Prevention of pneumococcal disease

- A pneumococcal polysaccharide vaccine currently is licensed and offers protection against invasive pneumococcal pneumonia. This vaccine is recommended primarily for use in the elderly and people with risk factors for pneumococcal disease; it is not recommended for children <2 years of age. It is unlikely that this vaccine will decrease the prevalence of pneumococcal resistance.
- A pneumococcal conjugate vaccine is currently undergoing Phase III clinical trials and licensure was anticipated by the year 2000. This vaccine induces immunity in children <2 years of age, and appears highly effective at preventing invasive disease due to the serotypes covered by the vaccine. The vaccine also has some efficacy against non-invasive pneumococcal disease, and reduces carriage of vaccine-serotypes. Although expensive, this vaccine has great potential to reduce the burden of pneumococcal disease in children, and to reduce carriage of antibiotic-resistant strains covered by the 7- and 11-valent formulations.
- Xylitol sugar reduces otitis media and antibiotic use by 30%.
- Reduced exposure to smoke may help reduce the risk of pneumococcal disease; vitamin A supplementation should be approached with caution because of observed adverse effects in some studies.

4. Research needs: Prevention of pneumococcal disease

1. The pneumococcal conjugate vaccine is the most promising intervention to date to reduce the burden of pneumococcal disease in children. Because the vaccine has the potential to reduce the incidence of pneumococcal disease and resistance, investigations of the impact of the conjugate vaccine should be a high research priority. Beyond clinical efficacy against invasive disease, a number of areas should be investigated once vaccine licensure is obtained:
 - Measure the efficacy of the vaccine at preventing carriage of vaccine-included serotypes
 - Assess the impact of vaccination on the prevalence of antibiotic-resistant *S. pneumoniae* in nasopharyngeal and invasive disease isolates
 - Determine whether non-vaccine serotypes replace vaccine serotypes in the nasopharynx
 - Determine whether invasive disease due to non-vaccine serotypes increases
 - Measure the efficacy of the vaccine at preventing acute otitis media and mild pneumonia
 - Assess whether vaccination reduces antibiotic use in children <5 years of age
 - Determine whether vaccination results in herd immunity.
2. Conduct large controlled clinical trials in developed and developing countries to assess the effectiveness of xylitol sugar at reducing acute otitis media and antibiotic use in children.

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Appendix

Participants in the Drug Resistant *S. pneumoniae* Therapeutic Working Group (DRSPTWG) consensus meeting on pneumococcal otitis media

- Dr David Bell, National Center for Infectious Diseases, Centers for Disease Control and Prevention
- Dr Robert Breiman, National Vaccine Program Office, Centers for Disease Control and Prevention
- Dr Daniel J. Burch, Pharmaceutical Research, Manufacturers Association
- Dr Jay C. Butler, Respiratory Diseases Branch, Centers for Disease Control and Prevention
- Dr Matthew Cartter, Council of State and Territorial Epidemiologists
- Dr Martin Cetron, Division of Quarantine, Centers for Disease Control and Prevention
- Dr Joan Chesney, American Academy of Pediatrics
- Dr William Craig, Infectious Diseases Society of America
- Dr Ron Dagan, Pediatric Infectious Disease Unit, Soroka Medical Center, Beer Sheva, Israel
- Dr Scott F. Dowell, Respiratory Diseases Branch, Centers for Disease Control and Prevention
- Dr Kathryn Edwards, Vanderbilt University
- Dr Kenneth Gershman, Council of State and Territorial Epidemiologists
- Dr Bruce Gellin, National Institutes of Health
- Dr G. Scott Giebink, Otitis Media Research Center, University of Minnesota Medical Center
- Dr Mary Gilchrist, Association of State and Territorial Public Health Laboratory Directors
- Dr Sheryl Henderson, Emory University
- Dr Michael Jacobs, Department of Pathology, Case Western Reserve University School of Medicine
- Dr Dan Jernigan, Washington State Department of Health
- Dr Ronald N. Jones, American Society for Microbiology; Dr James H. Jorgensen, NCCLS
- Dr Sheldon Kaplan, American Academy of Pediatrics
- Dr Jerome O. Klein, Maxwell Finland Lab for Infectious Diseases
- Dr Keith Klugman, South African Institute for Medical Research
- Dr Leah Raye Mabry, American Academy of Family Physicians
- Dr Daniel R. Martin, Society for Academic Emergency Medicine
- Dr William Martone, National Foundation for Infectious Diseases
- Dr Daniel M. Musher, American College of Physicians
- Dr Tom O'Brien, World Health Organization Network
- Dr Jack Paradise, Children's Hospital, Pittsburgh, PA; Dr Michael A. Pfaller, College of American Pathologists
- Dr Joseph F. Plouffe, Ohio State University Medical Center
- Dr Michael Poole, American Academy of Otolaryngology—Head and Neck Surgery
- Dr Alexander Rakowsky, Food and Drug Administration
- Dr Frederick Ruben, American Thoracic Society/American Lung Association
- Dr Benjamin Schwartz, Respiratory Diseases Branch, Centers for Disease Control and Prevention
- Dr Fred Tenover, Hospital Infections Program, Centers for Disease Control and Prevention
- Dr George Zhanel, Society of Infectious Disease Pharmacists.